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Third Edition

Current CANCER *Therapeutics*

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IRINOTECAN

Irinotecan (CPT-11) is a semisynthetic analogue of camptothecin with improved water solubility. Like its parent compound, irinotecan is an S-phase–specific inhibitor of DNA topoisomerase-I (topo-1). Topo-1 catalyzes the relaxation of the DNA molecule by introducing a transient break in one of the two strands of DNA. Inhibition of the enzyme leads to the stabilization of cleavable complexes formed by the enzyme and the DNA molecule, preventing the repair of the break caused by topo-1. This leads to the formation of single- and double-stranded DNA breaks and cell death by apoptosis. Irinotecan was the first drug in its class to be approved for clinical use.

Irinotecan acts as a prodrug and undergoes rapid partial conversion to its active metabolite, SN-38 (7-ethyl-1-hydroxy-camptothecin) through hydrolysis by cellular carboxyl esterase. SN-38 is 250 to 1000 times more potent than the parent compound. This reaction occurs in several body tissues, including the liver and the gastrointestinal tract. In equilibrium, it exists in two forms: an active lactone form favored at acidic pH and an inactive carboxyl form. In the plasma, SN-38 is found mainly in the lactone form.

DOSAGE AND ADMINISTRATION

Recommended starting dose: 125 mg/m^2 IV infusion over 90 min; one treatment course comprises 125 mg/m^2 once weekly for 4 wk followed by a 2-wk rest; the dose may be adjusted up to 150 mg/m^2 or down to 50 mg/m^2 depending upon patient tolerance; if tolerated, courses may be continued until disease progression; **In Europe:** the drug has been used at a dose of 350 mg/m^2 as a 30–90 min infusion once every 3 wk; other investigational schedules include once every 2 wk, once every 4 wk, and as a 5-d continuous infusion

SPECIAL PRECAUTIONS

IV administration: take care to avoid extravasation; flushing with sterile water and application of ice are recommended in case of extravasation; **diarrhea:** *early*—diarrhea, abdominal cramping, or diaphoresis occurring within 24 h of irinotecan administration should be treated with 0.25–1.0 mg atropine IV, unless clinically contraindicated; *late*—diarrhea occurring later than 24 h after administration should be treated with 4 mg of loperamide PO at the first sign of increased bowel frequency or loose stools, followed by 2 mg every 2 h until patient is diarrhea free for at least 12 h; elderly patients or those who have received prior pelvic or abdominal radiation are at increased risk of adverse events and should be closely monitored; **Hepatic dysfunction:** contraindicated if serum bilirubin > 2 mg/dL or transaminases > 3 times normal without liver metastases and > 5 times normal with liver metastases

INDICATIONS

FDA-approved: patients with metastatic colorectal carcinoma with disease progression, recurrence, or lack of response to 5-fluorouracil–based chemotherapy

PHARMACOKINETICS

Absorption: usually administered IV; **Peak plasma concentration:** with 350 mg/m^2 bolus, the mean peak of irinotecan plasma concentration is 7.7 µg/mL and 56 ng/mL for SN-38; AUC of irinotecan, but not SN-38, increases linearly with dose; maximum concentrations are seen in 1 h following a 90-min infusion; **Half-life:** mean terminal half-life is 8.8 h for irinotecan and 11.6 h for SN-38; **Protein binding:** irinotecan, 65%; SN-38, 95%; **Metabolism and excretion:** conversion of irinotecan to SN-38 occurs by carboxylesterase enzymes, primarily in the liver; glucuronidation of SN-38 occurs in the liver; total hepatic excretion is 25%–50%; urinary excretion is < 20%

DRUG INTERACTIONS

Potential for greater myelosuppression if used with other chemotherapeutic agents; caution in patients who have received prior abdominal/pelvic radiation

RESPONSE RATES

Metastatic colorectal cancer: European phase II study demonstrated response rates of 18.8% (chemotherapy naive patients) and 17.7% (previously treated patients) at a dose of 350 mg/m^2 once every 3 wk; median duration of response was 9.1 mo, and median survival was 10.6 mo; a recent North Central Cancer Treatment Group (US) phase II study of 121 patients at a dose of 125 mg/m^2 × 4 wk, followed by a 2-wk rest reported response rates of 13.3% in previously treated patients and 25.8% in previously untreated patients; **Non–small cell lung cancer:** phase II studies in Japan reported response rates of 31%–34% (previously untreated patients); response rates of 42%–54% were reported in combination therapy with cisplatin; neutropenia and diarrhea are dose limiting in these studies; overall response rates were 21.3% in a Japanese phase II study with etoposide and G-CSF; **Gastric cancer:** phase I-II study from Japan reported a response rate of 41.7% in 24 patients in combination with cisplatin; **Other:** irinotecan has shown activity against leukemia, non-Hodgkin's lymphoma, and ovarian, cervical, and small cell lung cancer

PATIENT MONITORING

Hematologic: CBC with differential and platelets prior to each dose; consider dose reduction by 25 mg/m for grade 2 toxicity and 50 mg/m^2 for grade 3 or 4 toxicity; withhold treatment until absolute neutrophil count is > 1500/mm^3 and platelets are 100,000/mm^3; **Diarrhea (early and late):** treatment should be withheld until diarrhea is resolved; for grade 3 (7–9 stools/d), reduce dose by 25 mg/m^2 and for grade 4 (> 10 stools/d), reduce dose by 50 mg/m^2

IRINOTECAN (Continued)

TOXICITIES

Gastrointestinal: diarrhea can occur early (within 24 h) or late (after 24 h); median time to onset of late diarrhea is about 11 d; factors that increase the risk of grade 3 or 4 diarrhea include a starting dose of 125 mg/m^2 as opposed to 100 mg/m^2, age > 65 y, and prior abdominal/pelvic irradiation (*see* Special Precautions for treatment); nausea and vomiting is uncommon with antiemetics (dexamethasone with 5-HT antagonist); **Hematologic:** leukopenia and neutropenia are common; neutropenic fever occurred in 3% of patients in clinical trials; thrombocytopenia and anemia are less common; **Hepatic:** grade 3–4 elevation of transaminases occur in ~10% of a patients, particularly in those with liver metastases; **Alopecia:** uncommon

NURSING INTERVENTIONS

Irinotecan should be diluted in a 5% dextrose or a 0.9% NaCl solution prior to administration; observation for early abdominal cramps, diaphoresis, or early diarrhea; *see* Special Precautions.

PATIENT INFORMATION

Diarrhea: strict instructions on loperamide schedule for late diarrhea (*see* Special Precautions); instruct patient to call physician if diarrhea does not resolve; avoid usage of drugs with laxative properties; **Pregnancy and breast feeding:** female patients should use birth control and avoid nursing while on treatment.

FORMULATION

Available as Camptosar (Pharmacia and Upjohn, Kalamazoo, MI)

5-mL single-dose vial containing 20 mg/mL irinotecan for IV injection.